REMARKS

Claims 8, 10, 11, 16, 26, 28, 29, and 37-51 were pending in the application. Claims 8, 11, 16, 26, 28, 29, and 37-51 have been canceled. New claims 52-70 have been added. Accordingly, upon entry of the instant amendment and response, claims 52-70 will be pending.

Support for the amendment to claims can be found throughout the claims and specification as originally filed. Additional support for new claims 52 and 63 can be found in Figure 9. Additional support for new claims 53-55 and 64-66 can found in Table II at page 25 of the specification. Additional support for new claim 56 can be found in the specification at page 9, lines 16-17. Additional support for new claims 59 and 69 can be found in the specification at page 8, lines 30. No new matter has been added.

Cancellations to the claims should in no way be construed as an acquiescence to any of the Examiner's rejections and were done *solely* to expedite the prosecution of the application. Applicant reserves the right to pursue the cancelled claims in this or a separate application(s).

The Pending Claims

Applicant was the first to discover that there are two forms of the dimeric lymphotoxin-β-receptor immunoglobulin (LT-β-R-Ig) fusion protein produced by transformed cells during normal cell culture conditions. One of these forms is biologically active and binds to its ligand with high affinity, while the other is biologically inactive and does not bind the ligand with high affinity.

The new claims presented herein are directed to compositions comprising active LT-β-R-Ig fusion proteins and inactive LT-β-R-Ig fusion proteins, ***wherein no more than 30% of the LT-β-R-Ig fusion proteins are inactive.*** New claims 53 and 64 are directed to compositions comprising active LT-β-R-Ig fusion proteins and inactive LT-β-R-Ig fusion proteins, ***wherein no more than 17% of the LT-β-R-Ig fusion proteins are inactive.*** New claims 54 and 65 are directed to compositions comprising active LT-β-R-Ig fusion proteins and inactive LT-β-R-Ig fusion proteins, ***wherein no more than 10% of the LT-β-R-Ig fusion proteins are inactive***, and new claims 55 and 66 describe compositions comprising active LT-β-R-Ig fusion proteins and inactive LT-β-R-Ig fusion proteins, ***wherein no more than 6% of the LT-β-R-Ig fusion proteins are inactive.***

Accordingly, the claimed LT-β-R-Ig-fusion protein compositions are enriched for the presence of biologically active LT-β-R-Ig-fusion proteins comprise. More specifically, the

claimed preparations and compositions comprise ***no more than 30% inactive LT-β-R-Ig fusion proteins.*** Such compositions were not taught or suggested in the art of record.

Rejection of claims 16 and 41 under 35 U.S.C. §102(b) in view of Degli-Esposti *et al.*

Claims 16 and 41 are rejected under 35 USC 102(b) as lacking novelty in view of Degli-Esposti *et al.* (1997) *J Immunol* 158:1756 (hereinafter Degli-Esposti). The Examiner alleges that the chromatographic purification of secreted LTβR-Fc proteins described in Degli-Esposti anticipates the claimed invention. Applicant respectfully traverses this rejection.

Applicant submits that neither previously pending claims 16 and 41 nor new claims 52-70 are anticipated by Degli-Esposti for the reasons set forth below. Applicant notes that claims 16 and 41 have been cancelled. The subject matter of new claims 52-70 is set forth above.

For the reasons stated below, it is Applicant's position that the Examiner has failed to establish a *prima facie* case of anticipation. "Anticipation requires a showing that each limitation of a claim is found in a single reference, either expressly or inherently." *Perricone v. Medicis Pharm. Corp.*, 432 F.3d 1368, 1376 (Fed. Cir. 2005). To show that the prior art "necessarily" functions in accordance with, or includes the claimed limitations, one must show more than a mere probability or possibility of the inherent feature's existence. *See SmithKline Beecham Corp. v. Apotex Inc.,* 403 F.3d 1331, 1346 (Fed. Cir. 2005). Therefore, "[i]nherency...may not be established by probabilities or possibilities. The mere fact that a certain thing *may* result from a given set of circumstances is not sufficient." *Mehl/Biophile v. Milgraum, M.D.,* 192 F.3d 1362 at 1365 (emphasis added) (quoting *Hansgirg v. Kemmer*, 102 F.2d 212, 214 (CCPA 1939)).

Degli-Esposti describes expression of LT-β-R-Fc in mammalian CVI/EBNA cells. The Examiner suggests that Degli-Esposti teaches a composition comprising at least 70% active proteins because Degli-Esposti supposedly describes purification steps which would result in the preparation of claims 16 and 41. In contrast to this suggestion, Applicant respectfully submits that the LT-β-R-Fc composition described in Degli-Esposti does not contain no more than 30% active LT-β-R-Fc, as required by the amended claims. ***The purification techniques described in Degli-Esposti equally purify inactive and active LT-β-R-Fc together from other proteins, i.e., the inactive and active forms of LT-β-R-Fc would***

not be separated resulting in a composition comprising no more than 30% inactive LT-β-R-Fc.

Degli-Esposti describes purification of LT-β-R-Fc using a *protein G-sepharose column*, and cites Fanslow *et al.* as teaching the purification techniques (see page 1757 under "Generation of soluble recombinant LTβR" of Degli-Esposti). Fanslow *et al.* describes purifying recombinant sCD40:Fc *using a protein A/G column* (copy of Fanslow *et al.* is enclosed herewith as Appendix A - see page 656, first column, fifth paragraph). Importantly, the protein G column described in Degli-Esposti (and the protein A/G column referenced by Fanslow) is known in the art to bind the Fc portion of an antibody, and therefore would bind the Fc region of the LT-β-R-Ig fusion protein. Objective evidence of this knowledge in the art is provided herewith as Appendix B, literature from Thermo Fisher Scientific Inc., a company that sells both Protein A and G products. As indicated in Appendix B, both protein A and protein G bind the Fc region of the immunoglobulin. Therefore, the affinity chromatography technique used by Degli-Esposti does not select for biologically active LT-β-R-Ig-fusion proteins, but instead selects ***all*** LT-β-R-Ig-fusion proteins based on the binding of the Fc portion of the fusion protein to a protein A/G column.

Moreover, Degli-Esposti describes cell culture at conventional temperatures, which, as described in Applicant's specification, results in 50% active and 50% inactive LT-β-R-Fc. In Table II of Applicant's specification, LT-β-R-Fc fusion proteins expressed at the conventional temperature, *i.e.,* 37°C, resulted in a preparation in which about 50% of the LT-β-R-Ig fusion proteins were biologically inactive (see Table II). Thus, by selecting merely for the Fc region of the LT-β-R-Fc, the Protein A/G column could result in a composition having 50% active and 50% inactive LT-β-R-Fc.

In sum, Applicant submits that the chromatography methods described in Degli-Esposti merely separate the LT-β-R-Fc, (active and inactive forms), from other cellular proteins and would not result in a composition enriched for the presence of ***active*** LT-β-R-Fc fusion proteins as required by new claims 52-70 (and previously pending claims 16 and 41). ***The chromatography technique used by Degli-Esposti may have purified the pool of LTβR-Ig-fusion proteins away from other proteins, but would still result in a composition in which only about 50% of the LTβR-Ig-fusion proteins were biologically active.***

In addition, Applicant notes that Degli-Esposti also does not teach a pharmaceutical composition, as required by new claims 58, 62, 67, and 69. Thus, Degli-Esposti fails to teach all of the elements of new claims 58, 62, 68, and 70.

The Examiner also asserts that "biologically active" is not adequately defined, and suggests that the term indicates the ability to induce an immunological response. Applicant submits that the Examiner has misconstrued the term "biologically active" as used in previously pending claims 16 and 41, as the term "active" is defined at page 9, lines 13-14 of the specification. The specification provides that the "active" form of the fusion protein binds ligand with high affinity. Applicant notes that the rejection of the claims under 35 USC 112, second paragraph with respect to the term "active" was overcome based on the Amendment and Response filed on February 20, 2004. It is inappropriate for the Examiner to construe the term "biologically active" to mean "capable of inducing an immunological response" when Applicant has clearly described the definition of the term "active" in the specification and has provided further comments regarding the claim language in previous Amendment and Responses, including the Amendment and Response filed on February 20, 2004 which overcame the rejection under 35 USC 112, second paragraph.

In view of all of the foregoing, Applicant submits that Degli-Esposti fails to anticipate the invention of new claims 52-70 or previously pending claims 16 and 41.

Rejection of claims 8, 10-11, 16, 26, 28-29 and 37-51 under 35 U.S.C. §103(a) over Ashkenazi *et al.* as evidenced by Invitrogen or Degli-Esposti *et al.* in view of Kaufmann *et al.*

The Examiner has rejected claims 8, 10-11, 16, 26, 28-29 and 37-51 as being unpatentable over Ashkenazi *et al.* (WO 98/25967; hereinafter Ashkenazi) as evidenced by Invitrogen Life Technologies Manual (*Baculodirect™ Baculovirus Expression System,* 2004; Version F: 1-64; hereinafter Invitrogen manual) or Degli-Esposti *et al.* (hereinafter Degli-Esposti) in view of Kaufmann *et al.* (Biotechnology and Bioengineering; 1999; 63(5):573-582). The Examiner states that Ashkenazi and Degli-Esposti "do not specifically teach a composition in which the fusion protein further comprises growth media" and that the references "fail to specifically teach the composition at reduced temperature." The Examiner asserts that these deficiencies are remedied by Kaufmann which teach "use of a model system in which CHO cells are used to express a SEAP protein cultured at a reduced temperature of 30 degrees Celcius." The Examiner further asserts that "[i]t would have been obvious to one of ordinary skill in the art at the time the invention was made to substitute the SEAP protein of Kaufmann with the fusion proteins provided by either Ashkenazi or Degli-Esposti, because

the prior art provides sufficient motivation to reduce the normal culturing temperature." Applicant respectfully traverses this rejection.

A proper *prima facie* obviousness rejection requires that there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. Additionally, there must be a reasonable expectation of success. Finally, the prior art reference (or references when combined) must teach or suggest all the claim limitations. *See* M.P.E.P. § 2143. Also, see *In re Vaeck*, 947 F.2d 488, 493, 20 U.S.P.Q.2d 1438, 1443 (Fed. Cir. 1991) (the teaching or suggestion to make the claimed combination and the reasonable expectation of success must both be found in the prior art, not in applicant's disclosure).

Applicant submits that neither previously pending claims 8, 10-11, 16, 26, 28-29 and 37-51 nor new claims 52-70 are obvious in view of Ashkenazi as evidenced by Invitrogen Life Technologies Manual or Degli-Esposti in view of Kaufmann *et al.* for the reasons set forth below. The subject matter of the new claims is set forth above. Applicant notes that claims 8, 10-11, 16, 26, 28-29 and 37-51 have been cancelled.

At the outset, Applicant notes that the Kaufmann reference, used by the Examiner to remedy the deficiencies of Ashkenazi, the Invitrogen manual, and Delgi-Esposti, did not publish until after the priority date of the instant application. The Kaufmann reference published on June 5, 1999, whereas application 60/112752 (to which the instant application claims priority) was filed on December 16, 1998. As such, the Kaufmann reference fails to qualify as a §102(a) reference as required by §103(a).

As set forth above, none of the cited references teach or suggest compositions that comprise ***no more than 30% biologically inactive LT-β-R-Ig fusion proteins.*** Therefore, as the cited references fail to teach or suggest all of the claimed limitations, as acknowledged by the Examiner, Applicant respectfully requests that the rejection be withdrawn.

Notwithstanding the above, and without acquiescing to the rejection, claims directed to HVEM-Ig fusion proteins, and dependent claims depending therefrom have been canceled.

In view of the above, Applicant respectfully submits that new claims 52-70 (as well as previously pending claims 8, 10-11, 16, 26, 28-29 and 37-51) are patentable over Ashkenazi as evidenced by Invitrogen Life Technologies Manual or Degli-Esposti in view of Kaufmann *et al.*.

Rejection of claims 8, 10-11, 16, 26, 28-29, 37-42, 44-47, and 49 under 35 U.S.C. § 112, 1st paragraph.

The Examiner has maintained the rejection of claims 8, 10-11, 16, 26, 28-29, 37-42, 44-47, and 49 under 35 U.S.C. § 112, first paragraph. The Examiner maintains that the phrase "at least 70% biologically active" is not supported in either the claims or specification. The Examiner states that "[t]hose of skill would find the determination of at least 70% an arbitrarily [sic] designation determined from the figure." Applicant respectfully traverses this rejection.

It is noted that claims 8, 10-11, 16, 26, 28-29, 37-42, 44-47, and 49 have been cancelled in order to expedite prosecution. Applicant maintains, however, that claims 8, 10-11, 16, 26, 28-29, 37-42, 44-47, and 49 are fully supported by the specification, including Figure 9, for the reasons of record.

With respect to new claims 52-70, Applicant submits these claims are also fully supported by the specification. New claims 52-70 describe compositions that comprise ***no more than 30% biologically inactive LT-β-R-Ig fusion proteins***. Figure 9 of the specification provides a graph showing experimental results obtained from mammalian cell cultures incubated at a range of temperatures, wherein incubation temperature (x-axis) is plotted against % dead, *i.e.,* inactive, hLTβR (y-axis). Specifically, culture at temperature of about 35°C yields a preparation in which only about 30% of the fusion protein is inactive, and the percentage of inactive fusion protein decreases, for example, to about 5% at a temperature of 28°C. Thus, Applicant respectfully submits that the written description requirement set forth under 35 U.S.C. § 112, first paragraph is satisfied in view of new claims 52-70, and that the rejection of claims 8, 10-11, 16, 26, 28-29, 37-42, 44-47, and 49 is rendered moot by their cancellation.

CONCLUSION

In view of the foregoing comments, reconsideration of the rejections and allowance of all pending claims is respectfully requested.

If a telephone conversation with Applicant's Attorney would expedite the prosecution of the above-identified application, the examiner is urged to call Applicant's Attorney at (617) 227-7400.

Respectfully submitted,

/ Cristin Cowles /

Cristin Howley Cowles, Ph.D.
Registration No. 55,281
Attorney for Applicant
LAHIVE & COCKFIELD, LLP
One Post Office Square
Boston, MA 02109
(617) 227-7400

Dated: May 2, 2008